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(54) 1-Aminoisoquinoline derivatives.

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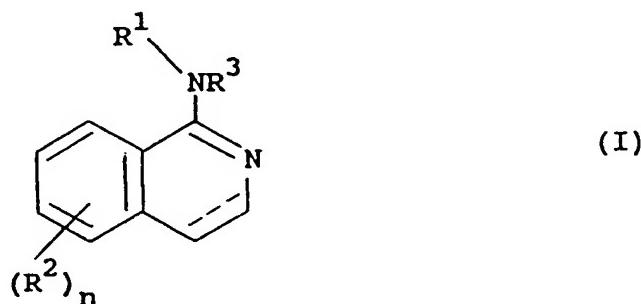
Description

The present invention relates to novel substituted isoquinoline derivatives, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy.

Substituted isoquinoline derivatives are known in the art. For example, FR-M-8482 discloses certain substituted isoquinoline derivatives as bronchodilating agents; and GB-A-1,244,501 discloses isoquinoline derivatives as anti-hypertensive agents. Such compounds are not, however, disclosed in the art as inhibitors of gastric acid secretion.

It has now been found that substituted isoquinoline derivatives are useful in therapy in the inhibition of gastric acid secretion.

Accordingly, the present invention provides, in a first aspect, the use of a compound of structure (I) :



in which

R¹ is C₁-₆alkyl, C₃-₆cycloalkyl, C₃-₆cycloalkylC₁-₆alkyl, phenyl(CH₂)_m the phenyl group being optionally substituted by 1-3 radicals selected from C₁-₆alkyl, C₁-₆alkoxy, amino C₁-₆alkylthio, halogen, cyano, hydroxy, carbamoyl, carboxy, C₁-₆alkanoyl and trifluoromethyl or Het(CH₂)_m in which Het is a 5 or 6 membered carbocyclic ring containing one or more heteroatoms and m is 0 to 6;

R² is C₁-₆alkyl, phenyl, C₁-₆alkoxy, C₁-₆alkylthio, hydroxy, C₁-₆alkanoyl, amino, C₁-₆alkylamino, di-C₁-₆alkylamino, halogen, trifluoromethyl or cyano;

R³ is hydrogen or C₁-₄alkyl;

n is 0, 1 or 2, and the dotted line indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the inhibition of gastric acid secretion.

Preferably R¹ is a substituted phenyl group or benzyl group. More preferably, R¹ is a phenyl or benzyl group substituted by a single substituent; in particular in the 2-position. Most preferably R¹ is a phenyl or benzyl group substituted in the 2-position by a C₁-₆alkyl group for example a methyl group.

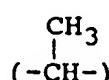
Suitably, n is 2 and one group R² is in the 7-position. Preferably n is 0; most preferably n is 1 and the group R² is in the 7-position; more preferably n is 0.

Suitably R² is C₁-₆alkylphenyl, C₁-₆alkylthio, C₁-₄alkanoyl, amino, C₁-₆alkylamino, diC₁-₆alkylamino, halogen, trifluoromethyl or cyano. Preferably R² is C₁-₆alkoxy, for example methoxy.

Suitably R³ is hydrogen or C₁-₄alkyl; preferably hydrogen.

C₁-₆alkyl groups (either alone or as part of another group) can be straight or branched.

Alkylene chains (CH₂)_m in which m is 1 to 6 include straight and branched chains. For example, ethylene or α-methylmethylenne



etc.

Heterocyclic groups Het, include for example, furanyl and thienyl groups; other standard groups will be apparent to those skilled in the art.

It will be appreciated that compounds of structure (I) in which one or more of R¹ or R² is a C₃-6alkyl group (either alone or as part of another group for example a benzyl or phenethyl group) may contain an asymmetric centre due to the presence of the C₃-5alkyl group. Such compounds will exist as two (or more) optical isomers (enantiomers/diastereoisomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the present invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

Compounds of structure (I) can form pharmaceutically acceptable acid addition salts with suitable organic and inorganic acids the nature of which will be apparent to persons skilled in the art. For example, pharmaceutically acceptable salts can be formed by reaction with hydrochloric, sulphuric, or phosphoric acids; aliphatic, aromatic or heterocyclic sulphonic acids or carboxylic acids such as for example, citric, maleic or fumaric acids. In particular, salts formed with such carboxylic acids, especially citric acid, have improved solubility characteristics when compared to the parent compound.

In a further aspect of the invention there is provided certain novel compounds falling within the scope of structure (I), that is to say, compounds of structure (IA):



(IA)

30

in which

R¹ is a phenyl or benzyl group, optionally substituted by a single substituent in the 2-position of the ring;

35 R² is C₁-6alkyl, phenyl, C₁-6alkoxy, C₁-6alkylthio, hydroxy, C₁-6alkanoyl, amino, C₁-6alkylamino, di-C₁-6alkylamino, halogen, trifluoromethyl or cyano;

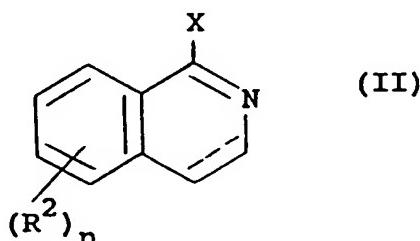
R³ is hydrogen or C₁-4alkyl;

n is 0, 1 or 2, and the dotted line indicates the optional presence of a double bond, or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a process for the preparation of a compound of structure (IA) which comprises

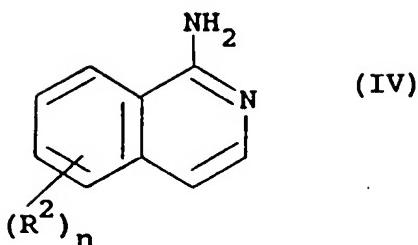
40 (a) reaction of a compound of structure (II) with a compound of structure (III) :

45



R¹R³NH (III)

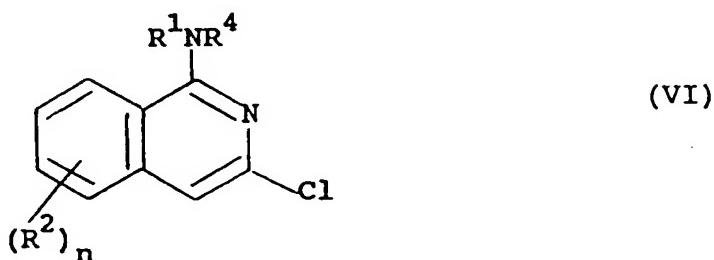
55 in which R¹, R², R³ and n are as described for structure (IA) and X is a group displaceable by an amine; (b) for compounds of structure (IA) in which a double bond is present and in which R¹ is optionally substituted benzyl and R³ is hydrogen reaction of a compound of structure (IV) with a compound of structure (V)



10 R¹X¹ (V)

in which R¹, R² and n are as described for structure (IA); R¹ is optionally substituted benzyl and X¹ is a leaving group; or

15 (c) for compounds of structure (IA) in which a double bond is present reduction of a compound of structure (VI)



in which R¹, R², and n are as described for structure (IA); and R⁴ is hydrogen or a nitrogen protecting group;

30 and thereafter if desired,

- removing any protecting groups;
- converting a group R¹ into another group R¹;
- forming a pharmaceutically acceptable salt.

Suitable groups X displaceable by an amine, include for example, aryl or alkylsulphonates, for example, toluene-p-sulphonate or methane sulphonate, alkylthio, alkylsulphonyl, alkylsulphanyl or alkoxy. Preferably X is a halo atom, for example, chloro or bromo, or an alkylthio group, in particular methylthio.

Suitable leaving groups X¹ will be apparent to those skilled in the art and include for example a halo moiety, preferably chloro or bromo.

Suitable nitrogen protecting groups R⁴ will be apparent to those skilled in the art for example as described in "Protective Groups in Organic Synthesis" T.W. Greene, 1981 (Wiley).

The reaction between compounds of structure (II) and compounds of structure (III) is carried out at elevated temperature optionally in the presence of an organic solvent. Suitable solvents include, for example, dimethylformamide, tetrahydrofuran, dioxan, ethanol or anisole. Preferably the reaction is carried out at elevated temperature under fusion conditions in the absence of a solvent.

45 The reaction between compounds of structure (IV) and compounds of structure (V) is carried out in an organic solvent at a temperature of between ambient and reflux temperature of the solvent used, preferably in the presence of a base. Suitable solvents include for example, lower alkanols such as ethanol. Suitable bases include for example, tertiary amine bases such as triethylamine.

The reduction of a compound of structure (VI) is carried out by for example hydrogenation, over a noble metal catalyst in a suitable solvent. Suitably the reaction is carried out over a palladium on carbon catalyst in ethanol as a solvent.

The intermediates of structure (II) and (IV) can be prepared by standard techniques.

The intermediates of structure (III) and (V) are commercially available or can be prepared by standard techniques.

55 The compounds of structure (I) and structure (IA) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of the gastrointestinal H⁺K⁺ATPase enzyme.

In a further aspect therefore the present invention provides compounds of structure (IA) and pharmaceutically acceptable salts thereof for use in therapy. The compounds of structure (I) and (IA) and their

pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are useful in the treatment of gastrointestinal diseases in mammals, in particular humans. Such diseases include, for example, gastric and duodenal ulcers, aspiration pneumonitis and Zollinger-Ellison Syndrome.

5 Further, the compounds of structure (I) and (IA) can be used in the treatment of other disorders where an anti-secretory effect is desirable for example in patients with gastritis, NSAID induced gastritis, acute upper intestinal bleeding, in patients with a history of chronic and excessive alcohol consumption, and in patients with gastro oesophageal reflux disease (GERD).

In addition to the foregoing use the compounds of structure (I) and (IA) can be expected to be of use in
10 medicine as inhibitors of bone resorption. In normal subjects there is a balance between bone resorption and bone formation, however in subjects with bone affected diseases such as osteoporosis, Paget's disease and hyperparathyroidism and related disorders this balance is disturbed. As a consequence the subject suffers a loss of bone tissue, decreased bone mass and bone fragility which can result in fracturing of
15 bones. Bone resorption (or bone loss) is associated with the activity of osteoclast cells, and it is thought that agents which inhibit the activity of such cells (and so inhibit bone resorption) will have a beneficial effect on the reduction of bone loss and be of benefit in the treatment of the above-noted disease states. The present compounds can be expected to be inhibitors of osteoclast activity and bone resorption and to be of use in medicine in the treatment of diseases in which bone loss is a factor, in particular osteoporosis, Paget's disease and hyperparathyroidism.

20 In therapeutic use, the compounds of structure (I) and (IA) are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (IA) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and (IA) and their pharmaceutically acceptable salts which are active
25 when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring
30 agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For
35 example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or (IA) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycals, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or (IA) or a pharmaceutically acceptable salt thereof calculated as the free base.

When used in therapy, for the treatment of gastrointestinal diseases and other conditions caused or exacerbated by gastric acidity, the daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or (IA) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more. In addition, the compounds of the present invention can be co-administered with further active ingredients, such as antacids (for example

magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-inflammatory drugs (for example indomethacin, aspirin or naproxen), steroids, or nitrite scavengers (for example ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example pirenzipine, prostanoids for example 16,16 dimethyl PGE₂, or histamine H₂-antagonists (for example, cimetidine).

5 The following examples illustrate the invention. Temperatures are recorded in degrees centigrade.

Example 1

1-[(2-Methylphenyl)amino]isoquinoline hydrochloride

10 1-Chloroisoquinoline (J.O.C. (1958), 23, 1071) (1.64 g, 0.01 mol) and o-toluidine (1.07 g, 0.01 mol) were heated together at reflux temperature in dry dioxan (20 ml) for 18 hours. After this time a light brown oil had precipitated in the hot solution. After cooling the mixture was evaporated to dryness to give an off-white, sticky solid. This was treated with diethyl ether (50 ml), collected, washed with ether and dried to give a
15 white solid (2.07 g). This solid was crystallised from ethanol/ ether to give the title compound (1.97 g) as its hydrochloride salt, m.p. 229-231°.

C ₁₆ H ₁₄ N ₂ . HCl				
Found	C 71.4, C 71.0,	H 5.7, H 5.6,	N 10.4, N 10.4,	Cl ⁻ 13.0%; Cl ⁻ 13.1%;
Requires				

25 Example 2

1-(Benzylamino)isoquinoline

30 1-chloroisoquinoline (1.64 g, 0.01 mol) and benzylamine (2.14 g, 0.02 mol) were mixed at room temperature and heated, with stirring, in an oil-bath at 50° for 4 hours. The mixture was cooled to give a crystalline solid which was equilibrated between methylene chloride (CH₂Cl₂) and aqueous Na₂CO₃. The CH₂Cl₂ fraction was washed with water, dried and evaporated to dryness to give an oil which crystallised on standing (3.0 g). This material was twice re-crystallised from ether/40-60 petroleum ether to give the title compound as buff crystals, m.p. 101-102°.

C ₁₆ H ₁₄ N ₂				
Found	C 82.0, C 82.0,	H 6.1, H 6.0,	N 12.1%; N 12.0%;	
Requires				

40

Example 3

1-[(2-Methylphenylmethyl)amino]isoquinoline hydrochloride

45 Substituting 2-methylbenzylamine (2.03 gm, 0.017 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 2 gave a brown oil (3.1 g). This was dissolved in the minimum amount of methanol and 2N HCl added to precipitate a buff-coloured solid which was collected, washed with water and dried (1.67 g).

50 Crystallisation from absolute ethanol gave the title compound as its hydrochloride salt, m.p. 244-248°.

C ₁₇ H ₁₆ N ₂ . HCl				
Found	C 71.6, C 71.7,	H 6.0, H 6.0,	N 9.8, N 9.8,	Cl ⁻ 12.3%; Cl ⁻ 12.5%;
Requires				

Example 4

1[(2-Methoxyphenyl)methyl]amino]isoquinoline

5 Substituting 2-methoxybenzylamine (1.67 g 0.0122 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 2 gave a brown oil which was dissolved in the minimum amount of methanol and aqueous 2NHCl added. The solution was basified with 2N. NaOH and the precipitated buff-coloured solid collected, washed with water and dried (1.60 g). This material was crystallised from methanol to give the title compound (1.0 g) as buff-coloured needles, m.p. 111-113°.

10

C ₁₇ H ₁₆ N ₂ O			
Found Requires	C 77.2, C 77.2,	H 6.1, H 6.1,	N 10.5%; N 10.6%:

15

Example 5

1-[N-Methylphenylmethylamino]isoquinoline

20 Substituting N-methylbenzylamine (1.48 g, 0.0122 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 2 gave a brown oil (2.42 g, may contain trace of CH₂Cl₂). This material was purified by column chromatography on silica gel using CH₂Cl₂ as eluting solvent to give a pale-green oil (0.82 g) which solidified on standing and was re-crystallised from ether/40-60 petroleum ether to give the title compound (0.76 g), m.p. 53.5-54.5°.

25

C ₁₇ H ₁₆ N ₂			
Found Requires	C 82.1, C 82.2,	H 6.4, H 6.5,	N 11.2%; N 11.3%;

30

Example 6

35

1-(2-Phenylethylamino)isoquinoline.

Substituting 2-phenylethylamine (1.48 g 0.0122 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 2 gave a brown oil which crystallised on standing (2.48 g).
40 This material was crystallised twice from ether/40-60 petroleum ether to give the title compound (1.03 g) as a white solid, m.p. 110-112°.

45

C ₁₇ H ₁₆ N ₂			
Found Requires	C 82.4, C 82.2,	H 6.7, H 6.5,	N 11.2%; N 11.3%;

50

Example 7(R)-(-)-1-[(α -Methylphenyl)methyl]amino]isoquinoline

55 Substituting R-(+)- α -methylbenzylamine (1.48 g, 0.0122 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 2 gave a brown oil which could not be crystallised. This material was chromatographed on silica gel using methylene chloride as eluting solvent. Fractions were monitored by thin-layer chromatography and those containing product were combined and evaporated to dryness to give an oil (0.6 g) which solidified on standing. Crystallisation from ether/40-60 petroleum ether gave the title compound (0.36 g) as pale-yellow crystals, m.p. 79-80°.

25°
 $[\alpha]_D = -204.6.$

5

$C_{17}H_{16}N_2$			
Found Requires	C 82.0, C 82.2,	H 6.5, H 6.5,	N 11.3%; N 11.3%;

10

Example 815 (S)-(+)-1-[$(\alpha$ -Methylphenylmethyl)amino]isoquinoline

Substituting S-(-)- α -methylbenzylamine (1.48 g 0.0122 mol) for R-(+)- α -methylbenzylamine and using corresponding molar proportions of the other reagents in Example 7 gave, after chromatography a crystalline solid (0.79 g). This material was re-crystallised from ether/40-60 petroleum ether to give the title compound (0.37 g), m.p. 81-83°.
20

25°
 $[\alpha]_D = +205.7.$

25

$C_{17}H_{16}N_2$			
Found Requires	C 82.1, C 82.2,	H 6.5, H 6.5,	N 11.3%; N 11.3%;

30

Example 9

35 1-[(4-Methoxyphenylmethyl)amino]isoquinoline

Substituting 4-methoxybenzylamine (3.34 g, 0.0244 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 2 gave a green oil which could not be crystallised. This material was chromatographed on silica gel using CH_2Cl_2 as eluting solvent. Fractions containing product 40 were combined and evaporated to dryness to give a green oil (1.6 g). This was crystallised from ether/40-60 petroleum ether to give the title compound (1.07 g) as a colourless crystalline solid, m.p. 55-56°.

$C_{17}H_{16}N_2O$			
Found Requires	C 77.4, C 77.3,	H 6.0, H 6.1,	N 10.6%; N 10.6%;

50

Example 10

55 1-[(2-Thienylmethyl)amino]isoquinoline

Substituting 2-thiophenemethylamine (1.39 g, 0.0122 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 2 gave a brown oil which solidified on scratching (1.25 g). This material could not be satisfactorily crystallised so it was chromatographed on silica gel using CH_2Cl_2 as eluent. Fractions containing major product (t.l.c.) were combined and evaporated to dryness to give an oil which solidified on standing (0.9 g). This material was crystallised twice from ether/40-60 petroleum ether to give the title compound (0.6 g) as orange-yellow crystals, m.p. 86.5-87.5°.

5

C ₁₄ H ₁₂ N ₂ S			
Found	C 70.5, C 70.0,	H 5.0, H 5.0,	N 11.7%; N 11.7%;

10

Example 11

1-[{(2-Furylmethyl)amino]isoquinoline

Substituting furfurylamine (1.2 g, 0.0122 mol) for 2-thiophenemethylamine and using corresponding molar proportions of the other reagents in Example 10 gave, after similar chromatography, a pale-orange oil which solidified on scratching (1.14 g). This material was crystallised twice from ether/40-60 petroleum ether to give the title compound (0.76 g) as pale-pink crystals, m.p. 76-77°.

15

20

C ₁₄ H ₁₂ N ₂ O			
Found	C 75.1, C 75.0,	H 5.3, H 5.4,	N 12.5%; N 12.5%;

Example 12

25 5-Methoxy-1-[(benzylmethyl)amino]isoquinoline hydrochloride

5-Methoxy-1-chloroisoquinoline (J.A.C.S. (1947), 69, 1939) (1.5 g, 0.00777 mol) and benzylamine (1.67 g, 0.0156 mol) were mixed at room temperature and heated, with stirring, in an oil-bath at 150° for 4 hours. After cooling the mixture was equilibrated between CH₂Cl₂ and aqueous Na₂CO₃. The CH₂Cl₂ fraction was washed with water, dried and evaporated to dryness. The oil produced was dissolved in the minimum amount of methanol and aqueous 2N. HCl added to precipitate a buff solid which was collected, washed with water and dried (2.15 g). This material was crystallised from ethanol/methanol to give the title compound (1.40 g) as its hydrochloride salt, m.p. 247-252° (Dec).

35

C ₁₇ H ₁₆ N ₂ O. HCl				
Found	C 67.9, C 67.9,	H 5.7, H 5.7,	N 9.3, N 9.3,	Cl ⁻ 11.9%; Cl ⁻ 11.8%;

40

Example 13

45 5-Methoxy-1-[(2-methylphenyl)amino]isoquinoline

5-methoxy-1-chloroisoquinoline (1.5 g, 0.00777 mol) and o-toluidine (0.835 gm, 0.00777 mol) were mixed in anisole (10 ml) and heated with stirring in an oil-bath at 140° for four hours. After cooling the mixture was dissolved in methanol and ether was added to precipitate a tacky solid. The solvent was decanted off and the precipitate washed with more ether. The insoluble residue was equilibrated between N. HCl and ether, the aqueous acid solution filtered and basified with saturated aqueous Na₂CO₃ to precipitate a buff solid which was collected, washed with water and dried (0.77 g). This material was crystallised from diethyl ether to give the title compound (0.62 g) as fluffy, light-buff needles, m.p. 111-112°.

55

C ₁₇ H ₁₆ N ₂ O. 0.15 Et ₂ O.			
Found	C 76.5, C 76.7,	H 6.4, H 6.4,	N 10.2%; N 10.2%;

Example 14

5-Methoxy-1-[(2-methylphenylmethyl)amino]isoquinoline

5 Substituting 2-methylbenzylamine (1.25 g, 0.01033 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 12 produced, after equilibration between aqueous Na₂CO₃ and CH₂Cl₂ and drying and evaporation of the organic phase a light brown solid (1.09 g). This material was crystallised from ethanol/H₂O to give the title compound (0.7 g) as its partial hydrate, m.p. 121-125° (Not sharp).

10

C ₁₈ H ₁₈ N ₂ O. 0.2H ₂ O				
Found Requires	C 76.8, C 76.8,	H 6.6, H 6.6,	N 9.9%; N 10.0%;	

15

Example 15

20 1-[(2-Methoxyphenylmethyl)amino]-6,7-dimethoxyisoquinoline hydrochloride

25 6,7-Dimethoxy-1-chloroisoquinoline (J. Am. Pharm. Assoc., Sci. Ed. (1952), 41, 643-50; C.A. 47, 11205d.) (1.0 gm, 0.00447 mol) and 2-methoxybenzylamine (1.22 gm, 0.00894 mol) were mixed at room temperature and heated, with stirring, in an oil-bath at 140° for 1.5 hours. After cooling the mixture was dissolved in chloroform and the solution washed with saturated NaHCO₃ solution and water, dried and evaporated. The resulting oil was chromatographed on silica gel, using chloroform as eluent. Fractions were monitored by t.l.c. and those containing pure product were combined, evaporated to dryness and the residue (0.25 g) dissolved in ethanol containing ethanolic hydrogen chloride. This solution was evaporated to dryness and the residue crystallised from ethanol/diethyl ether to give the title compound as its hydrochloride salt (0.22 gm), m.p. 225-229°.

30

35

C ₁₉ H ₂₀ N ₂ O ₃ . HCl. 0.25H ₂ O				
Found Requires	C 62.3, C 62.5,	H 5.8, H 5.9,	N 7.5, N 7.7,	Cl ⁻ 9.8%; Cl ⁻ 9.7%;

Example 16

40 1-[(2-Methylphenyl)amino]-6,7-dimethoxyisoquinoline hydrochloride

45 Substituting o-toluidine (1.91 g, 0.0178 mol) for 2-methoxybenzylamine and using corresponding molar proportions of other reagents in Example 15 produced, after column chromatography, an oil (0.54 gm). This was dissolved in ethanolic hydrogen chloride, the solution evaporated to dryness and the residue crystallised from ethanol/diethyl ether to give the title compound as its hydrochloride salt (0.40 g), m.p. 253-255°.

50

C ₁₈ H ₁₈ N ₂ O ₂ . HCl. 0.2 H ₂ O				
Found Requires	C 64.4, C 64.6,	H 5.8, H 5.8,	N 8.1, N 8.4,	Cl ⁻ 10.3%; Cl ⁻ 10.6%;

Example 17

55 1-[(2-Methoxyphenylmethyl)amino]-6-methoxyisoquinoline hydrochloride.

6-Methoxy-1-chloroisoquinoline (JACS. (1947), 69, 1939) (1.65 g, 0.0085 mol) and 2-methoxybenzylamine (2.33 g, 0.017 mol) were mixed at room temperature and stirred in an oil-bath at 140° for 2 hours.

After cooling the solid mass was dissolved in chloroform and the solution washed with saturated NaHCO_3 - (x3) and water, dried and evaporated to give a pale-orange oil (2.3 g). This was dissolved in ethanol, ethanolic hydrogen chloride added and the solution evaporated to dryness. The residual solid was crystallised from ethanol/diethyl ether to give the title compound as its hydrochloride salt (1.24 g), m.p. 222-227°.

5

10

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$				
Found Requires	C 64.3, C 64.5,	H 5.7, H 5.9,	N 8.2, N 8.3,	Cl^- 10.5%; Cl^- 10.6%;

Example 18

15

1-[(2-Methylphenyl)amino]-6-methoxyisoquinoline hydrochloride

Substituting o-toluidine (1.37 g, 0.0128 mol) for 2 methoxybenzylamine and using corresponding molar proportions of other reagents in Example 17 gave, after equilibration of the product between aqueous NaHCO_3 and CHCl_3 a dark-orange oil (1.6 g). This was chromatographed on silica gel using chloroform as eluent to give a pale-yellow oil (0.5 g). This was dissolved in ethanolic hydrogen chloride, the solution evaporated to dryness and the residue crystallised from ethanol/diethyl ether to give the title compound as its hydrochloride salt (0.4 g), m.p. 230-240°.

25

$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O} \cdot \text{HCl} \cdot 0.1\text{H}_2\text{O}$				
Found Requires	C 67.3, C 67.5,	H 5.6, H 5.7,	N 9.2, N 9.3,	Cl^- 11.4%; Cl^- 11.7%;

30

Example 19

1-[(2-Methoxyphenylmethyl)amino]-7-methoxyisoquinoline hydrochloride

35

7-Methoxy-1-chloroisooquinoline (JACS, (1947), 69, 1939) (1.5 g, 0.00775 mol) and 2-methoxybenzylamine (2.12 g, 0.015 mol) were mixed at room temperature and heated with stirring in an oil-bath at 140° for 2 hours. After cooling the solidified mass was equilibrated between chloroform and saturated aqueous NaHCO_3 . The chloroform solution was washed with water, dried and evaporated to dryness to produce an oil which was chromatographed on silica gel using chloroform as eluent. Monitoring fractions by t.l.c. and H.P.L.C. and combination of appropriate samples gave, after evaporation, a buff-coloured oil (0.58 g). This was dissolved in ethanolic hydrogen chloride, the solution evaporated to dryness and the residue crystallised from ethanol/ether to give a buff solid (0.54 g). This was re-crystallised from ethanol/ether, with charcoaling, to give the title compound as its white hydrochloride salt (0.35 g), m.p. 197-201°.

45

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$				
Found Requires	C 63.3, C 63.6,	H 6.0, H 5.9,	N 8.1, N 8.2,	Cl^- 10.6%; Cl^- 10.4%;

50

Example 20

1-[(2-Methylphenyl)amino]-7-methoxyisoquinoline hydrochloride

55

Substituting o-toluidine (1.01 g, 0.0095 mol) for 2-methoxybenzylamine and using corresponding molar proportions of other reagents in Example 19 gave, after column chromatography (silica gel, CHCl_3 eluent) a pale-yellow oil (0.6 g). This oil was dissolved in ethanol, ethanolic hydrogen chloride added and the solution evaporated to dryness. The solid produced was crystallised from ethanol/diethyl ether to give the title

compound as its hydrochloride salt (0.4 g), m.p. 150-152°.

$C_{17}H_{16}N_2O \cdot HCl \cdot H_2O$					
	Found	C 64.0, C 64.0,	H 5.6, H 6.0,	N 8.8, N 8.8,	Cl⁻ 11.1% Cl⁻ 11.1%
5	Requires				

10 Example 21

1-Benzylamino-3,4-dihydroisoquinoline hydrochloride.

15 1-Methylthio-3,4-dihydroisoquinoline hydroiodide (J. Het. Chem. (1979), 16, 1313-1316) (0.9 g, 0.00295 mol), benzylamine (0.32 g, 0.00299 mol) and dry dimethylformamide (10 ml) were mixed at room temperature and heated with stirring in an oil-bath for 1 hour at 110°. The mixture was cooled and poured onto water (100 ml) to give a clear solution (pH = 8). This solution was basified with 2N. NaOH (pH = 11), and extracted with ethyl acetate (x 2). The ethyl acetate solution was washed with water, dried and evaporated to give a colourless oil. This material was dissolved in ethanol/ether and anhydrous ethanolic HCl added. On standing in the cold a white solid crystallised and was collected (0.9 g). This material was re-crystallised twice from ethanol/ether to give the title compound (0.53 g) as its slightly green hydrochloride salt, m.p. 229-232°.

$C_{16}H_{16}N_2 \cdot HCl$					
	Found	C 70.5, C 70.5,	H 6.2, H 6.3,	N 10.2, N 10.3,	Cl⁻ 13.2%; Cl⁻ 13.0%;
25	Requires				

30 Example 22

1-[(2-Methylphenylmethyl)amino]-3,4-dihydroisoquinoline hydroiodide.

35 1-Methylthio-3,4-dihydroisoquinoline hydroiodide (1.52 g, 0.005 mol) was dissolved in a solution of ethanol (50 ml) containing 2-methylbenzylamine (0.61 g, 0.005 mol). The colourless solution was heated at reflux temperature for six hours with effluent gases being passed through a CHLOROS trap. The solution was then cooled and stood in the refrigerator overnight to give white crystals (1.38 g). This material was crystallised from methanol/ ethanol to give the title compound (1.06 g) as its hydroiodide salt, m.p. 241-243°.

40

$C_{17}H_{18}N_2 \cdot HI$					
	Found	C 53.8, C 54.0,	H 5.0, H 5.1,	N 7.4, N 7.4,	I⁻ 34.3%; I⁻ 33.6%;
45	Requires				

Example 23

50 1-[(4-Hydroxyphenylmethyl)amino]-3,4-dihydroisoquinoline

55 1-Methylthio-3,4-dihydroisoquinoline hydroiodide (0.6 g, 0.00197 mol) and 4-hydroxybenzylamine (0.24 g, 0.00195 mol) were heated together at reflux temperature in ethanol (25 ml) for five hours. Effluent gases were passed through a CHLOROS trap. The mixture was then cooled and the ethanol evaporated off at reduced pressure. The tacky residue was dissolved in dilute HCl and the solution extracted with ethyl acetate. The clear aqueous solution was basified with 6N. NaOH and re-extracted with ethyl acetate. The latter organic extract was washed with water, dried and evaporated to dryness to give a white sticky solid. This was treated with ether and the ether decanted off. The residual solid was crystallised from absolute ethanol to give the title compound (0.11 g) as white crystals, m.p. 177-179°.

C ₁₆ H ₁₆ N ₂ O. 0.1 H ₂ O			
Found	C 75.2, C 75.6,	H 6.5, H 6.4,	N 10.8%; N 11.0%;

5

Example A

10 A tablet for oral administration is prepared by combining

	Mg/Tablet
Compound of structure (I)	100
lactose	153
Starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	<u>330 mg</u>

20

into a 9 mm tablet.

Example B

25

An injection for parenteral administration was prepared from the following

	%w:w
Compound of structure 1 1M citric acid sodium hydroxide (qs) water for injection EP	0.50% (w:v) 30% (v:v) to pH 3.2 to 100 ml

30

35 The compound of structure 1 was dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution was then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

40

Biological Data.(A) H⁺K⁺ATPase Activity.45 The effects of a single high concentration (100 μM) of a compound of structure (I) on K-stimulated ATPase activity in lyophilised gastric vesicles was determined. Preferred compounds of structure (I) were also tested over a range of concentrations to determine IC₅₀ values.(i) Preparation of lyophilised gastric vesicles (H/K-ATPase).

50 Lyophilised gastric vesicles were prepared from pig fundic mucosa after the method of Keeling et. al. (Biochem. Pharmacol., 34, 2967, 1985).

(ii) K⁺-stimulated ATPase activity.55 K⁺-stimulated ATPase activity was determined at 37° in the presence of the following : 10 mM Pipes/Tris buffer pH 7.0, 2 mM MgSO₄, 1 mM KCl, 2 mM Na₂ATP and 3-6 μg protein/ml lyophilised gastric vesicles. After incubation for 30 minutes, the inorganic phosphate hydrolysed from ATP was determined by the method of Yoda and Hokin (Biochem. Biophys. Res. Commun. 40, 880, 1970).

Compounds of structure (I) were dissolved in dimethylsulphoxide which up to the highest concentration used had no effect on K⁺-stimulated ATPase activity.

The effect of the highest concentration of each compound of structure (I) on the recovery of a standard amount of inorganic phosphate was also determined.

5

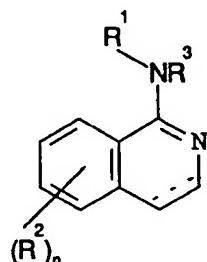
(iii) Results.

The compounds of examples 1 to 4 and 6 to 23 gave IC₅₀ values in the range of from 0.48 to 60 μM.

10 **Claims**

1. The use of a compound of structure (I):

15



20

25 (I)

in which

30 R¹ is C₁-₆alkyl, C₃-₆cycloalkyl, C₃-₆cycloalkylC₁-₆alkyl, phenyl(CH₂)_m the phenyl group being optionally substituted by 1-3 radicals selected from C₁-₆alkyl, C₁-₆alkoxy, amino, C₁-₆alkylthio, halogen, cyano, hydroxy, carbamoyl, carboxy, C₁-₆alkanoyl and trifluoromethyl or Het-(CH₂)_m in which Het is a 5 or 6 membered carbocyclic ring containing one or more heteroatoms and m is 0 to 6;

35 R² is C₁-₆alkyl, phenyl, C₁-₆alkoxy, C₁-₆alkylthio, hydroxy, C₁-₆alkanoyl, amino, C₁-₆alkylamino, di-C₁-₆alkylamino, halogen, trifluoromethyl or cyano;

R³ is hydrogen or C₁-₄alkyl;

n is 0, 1 or 2, and the dotted line indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of gastric acid secretion.

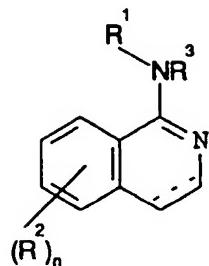
40

2. The use according to claim 1 in which R¹ is a phenyl or benzyl group substituted by a single substituent in the 2-position.
3. The use according to claim 2 in which the substituent is a C₁-₆alkyl group.
- 45 4. The use according to claim 1 which is 1-[(2-methoxyphenyl)methyl]amino]isoquinoline hydrochloride, 1-[(2-methylphenyl)amino]-7-methoxyisoquinoline hydrochloride.

50

55

5. A compound of structure (IA):



(IA)

15

in which

R¹ is a phenyl or benzyl group, optionally substituted by a single substituent in the 2-position of the ring;

20 R² is C₁-6 alkyl, phenyl, C₁-6 alkoxy, C₁-6 alkylthio, hydroxy, C₁-6 alkanoyl, amino, C₁-6 alkylamino, di-C₁-6 alkylamino, halogen, trifluoromethyl or cyano;

R³ is hydrogen or C₁-4 alkyl;

n is 0, 1 or 2, and the dotted line indicates the optional presence of a double bond, or a pharmaceutically acceptable salt thereof.

25

6. A compound according to claim 5 in which, in R¹, the single substituent is a C₁-6 alkyl group.

7. A compound according to claim 5 which is 1-[(2-methoxyphenylmethyl)amino]isoquinoline hydrochloride, 1-[(2-methylphenyl)amino]-7-methoxyisoquinoline hydrochloride.

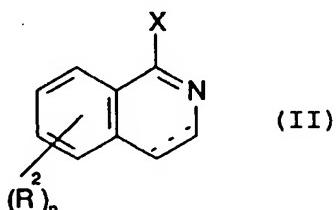
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8. A pharmaceutical composition comprising a compound according to any one of claims 5 to 7 and a pharmaceutically acceptable carrier.

9. A compound according to any one of claims 5 to 7 for use in therapy.

35

10. A process for the preparation of a compound according to claim 5 which comprises (a) reaction of a compound of structure (II) and a compound of structure (III):

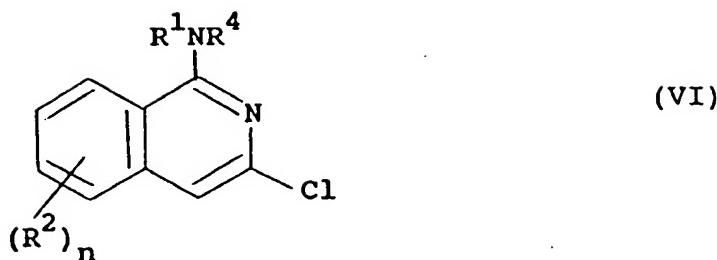


(II)

40

R¹R³NH (III)

50 in which R¹, R² and n are as described for structure (IA) and X is a group displaceable by an amine; (b) for compounds of structure (IA) in which a double bond is present and in which R¹ is optionally substituted phenyl(CH₂)_m and R³ is hydrogen reaction of a compound of structure (IV) with a compound of structure (V); (c) for compounds of structure (IA) in which a double bond is present reduction of a compound of structure (VI)



10

in which R¹, R², and n are as described for structure (IA); and R⁴ is hydrogen or a nitrogen protecting group;

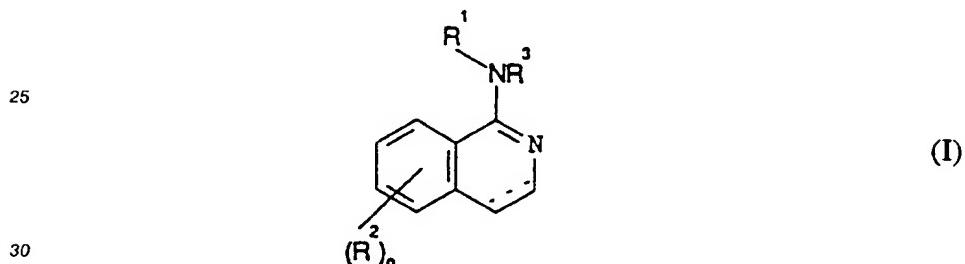
and thereafter if desired,

15

- removing any protecting groups;
- converting a group R¹ into another group R¹;
- forming a pharmaceutically acceptable salt.

Patentansprüche

20 1. Verwendung einer Verbindung der Struktur (I):



30 in der

R¹ ein (C₁-₆)Alkyl-, (C₃-₆)Cycloalkyl-, (C₃-₆)Cycloalkyl(C₁-₆)alkyl- oder Phenyl(CH₂)_m-rest ist, wobei die Phenylgruppe gegebenenfalls durch 1-3-Reste substituiert sein kann, die ausgewählt sind aus (C₁-₆)Alkyl, (C₁-₆)Alkoxy, Amino, (C₁-₆)Alkylthio, Halogen, Cyano, Hydroxy, Carbamoyl, Carboxy, (C₁-₆)Alkanoyl und Trifluormethyl, oder ein Rest Het(CH₂)_m, worin Het ein 5- oder 6-gliedriger carbocyclischer Ring ist, der ein oder mehrere Heteroatom(e) enthält, und m 0 bis 6 ist;

R² ein (C₁-₆)Alkyl-, Phenyl-, (C₁-₆)Alkoxy-, (C₁-₆)Alkylthio-, Hydroxy-, (C₁-₆)Alkanoyl-, Amino-, (C₁-₆)Alkylamino-, Di(C₁-₆)alkylamino-, Halogen-, Trifluormethyl- oder Cyanrest ist;

R³ ein Wasserstoffatom oder ein (C₁-₄)Alkylrest ist;

n 0, 1 oder 2 ist, und die gestrichelte Linie die optionale Anwesenheit einer Doppelbindung anzeigt;

oder ein pharmazeutisch verträgliches Salz davon zur Herstellung eines Arzneimittels zur Verwendung bei der Magensäuresekretionshemmung.

2. Verwendung gemäß Anspruch 1, in dem R¹ eine durch einen einzelnen Substituenten in 2-Stellung substituierte Phenyl- oder Benzylgruppe ist.

3. Verwendung gemäß Anspruch 2, in dem der Substituent ein (C₁-₆)Alkylrest ist.

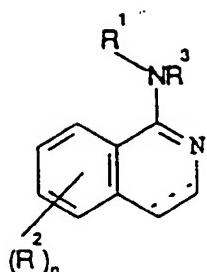
4. Verwendung gemäß Anspruch 1, nämlich von 1-[(2-Methoxyphenylmethyl)amino]isochinolinhydrochlorid oder 1-[(2-Methylphenyl)amino]-7-methoxyisochinolinhydrochlorid.

55

5. Verbindung der Struktur (IA):

5

10



(IA)

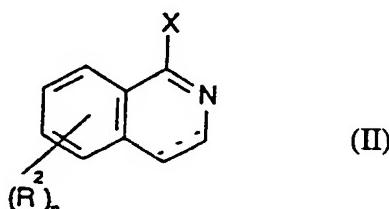
in der

- 15 R¹ eine Phenyl- oder Benzylgruppe bedeutet, die gegebenenfalls durch einen einzelnen Substituenten in 2-Stellung des Ringes substituiert ist;
 R² einen (C₁-₆)Alkyl-, Phenyl-, (C₁-₆)Alkoxy-, (C₁-₆)Alkylthio-, Hydroxy-, (C₁-₆)Alkanoyl-, Ami-
 no-, (C₁-₆)Alkylamino-, Di(C₁-₆)alkylamino-, Halogen-, Trifluormethyl- oder Cyanrest bedeutet,
 20 R³ ein Wasserstoffatom oder (C₁-C₄)Alkylrest ist;
 n 0, 1 oder 2 ist, und die gestrichelte Linie die optionale Anwesenheit einer Doppelbindung
 anzeigen,
 oder ein pharmazeutisch verträgliches Salz davon.

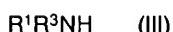
- 25 6. Verbindung gemäß Anspruch 5, in der der einzelne Substituent in R¹ eine (C₁-₆)-Alkylgruppe ist.
 7. Verbindung gemäß Anspruch 5, nämlich 1-[(2-Methoxyphenylmethyl)amino]isoquinolinhydrochlorid oder
 1-[(2-Methylphenyl)amino]-7-methoxyisoquinolinhydrochlorid.
 30 8. Arzneimittel, die eine Verbindung gemäß einem der Ansprüche 5 bis 7 und einen pharmazeutisch
 verträglichen Träger umfaßt.
 9. Verbindung gemäß einem der Ansprüche 5 bis 7 zur therapeutischen Verwendung.
 35 10. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 5, das umfaßt:
 (a) die Umsetzung einer Verbindung der Struktur (II) mit einer Verbindung der Struktur (III):

40

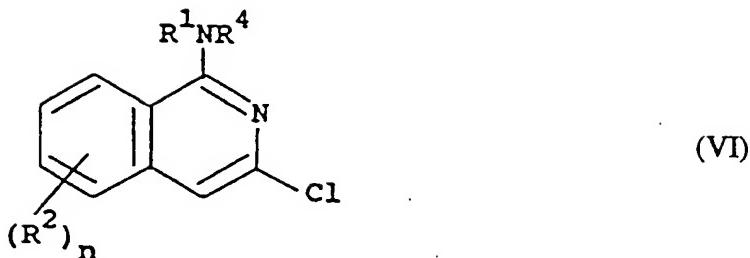
45



(II)



- 50 in denen R¹, R² und n wie für Struktur (IA) beschrieben sind und X ein durch ein Amin ersetzbarer
 Rest ist;
 b) für Verbindungen der Struktur (IA), in der sich eine Doppelbindung befindet und in der R¹ ein
 gegebenenfalls substituierter Phenyl(CH₂)_m-rest ist und R³ ein Wasserstoffatom bedeutet, Umset-
 zung einer Verbindung der Struktur (IV) mit einer Verbindung der Struktur (V):
 (c) für Verbindungen der Struktur (IA), in denen sich eine Doppelbindung befindet, Reduktion einer
 55 Verbindung der Struktur (VI):



10 in der R¹, R² und n wie für Struktur (IA) beschrieben sind und R⁴ ein Wasserstoffatom oder eine
Stickstoffschutzgruppe darstellt;
und danach, falls erwünscht,
• Entfernen der Schutzgruppen;
15 • Umwandlung eines Restes R¹ in einen anderen Rest R¹;
• Bilden eines pharmazeutisch verträglichen Salzes.

Revendications

20 1. Utilisation d'un composé de structure (I):



(I)

35 dans lequel

- R¹ est un groupe alkyleC₁-₆, cycloalkyleC₃-₆, cycloalkylC₃-₆ alkyleC₁-₆, phényle(CH₂)_m, le groupe phényle étant éventuellement substitué par 1 à 3 radicaux choisis parmi les groupes alkyleC₁-₆, alcoxyC₁-₆, amino, alkylC₁-₆thio, halogène cyano, hydroxy, carbamoyle, carboxy, 40 alcanoyleC₁-₆, et trifluorométhyle, ou un groupe Het(CH₂)_m dans lequel Het est un cycle carboné à 5 ou 6 atomes comportant un ou plusieurs hétéroatomes, et m un entier compris entre 0 et 6;
- R² est un groupe alkyleC₁-₆, phényle, alcoxyC₁-₆, alkylC₁-₆thio, hydroxy, alcanoyleC₁-₆, amino, alkylC₁-₆amino, dialkylC₁-₆amino, halogène, trifluorométhyle ou cyano;
- R³ est un atome d'hydrogène ou un groupe alkyle C₁-₄;
- n est égal à 0, 1, ou 2, et le trait interrompu indique la présence éventuelle d'une double liaison; ou d'un sel de celui-ci, acceptable du point de vue pharmaceutique, dans la fabrication d'un médicament pour l'inhibition de la sécrétion gastrique.

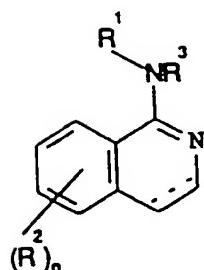
- 45
- 50
- 55
2. Utilisation suivant la revendication 1, pour laquelle R¹ est un groupe phényle ou benzyle substitué par un substituant unique en position 2.
 3. Utilisation suivant la revendication 2, pour laquelle le substituant est un groupe alkyleC₁-₆.
 4. Utilisation suivant la revendication 1, dans laquelle le composé est le chlorhydrate de 1-[(2-méthoxyphényleméthyl)amino]isoquinoléine, le chlorhydrate de 1-[(2méthylphényl)amino]-7-méthoxyisoquinoléine.

5. Composé de structure (IA):

5

10

15



(IA)

dans lequel

- R¹ est un groupe phényle ou benzyle éventuellement substitué par un substituant unique en position 2 du cycle;
- R² est un groupe alkyleC₁-₆, phényle, alcoxyC₁-₆, alkylC₁-₆thio, hydroxy, alcanoyleC₁-₆, amino, alkylC₁-₆amino, dialkylC₁-₆amino, halogène, trifluorométhyle ou cyano;
- R³ est un atome d'hydrogène ou un groupe alkyleC₁-₄;
- n est égal à 0, 1, ou 2, et le trait interrompu indique la présence éventuelle d'une double liaison; ou d'un sel de celui-ci, acceptable du point de vue pharmaceutique.

25

6. Composé suivant la revendication 5 dans lequel, dans R₁, le substituant unique est un groupe alkyleC₁-₆.

7. Composé suivant la revendication 5, qui est le chlorhydrate de 1-[(2-méthoxyphénylméthyl)amino]-isoquinoléine, le chlorhydrate de 1-[(2-méthylphényl)amino]-7-méthoxyisoquinoléine.

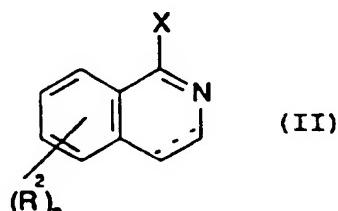
8. Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 5 à 7 et un véhicule, acceptable du point de vue pharmaceutique.

35 9. Composé suivant l'une quelconque des revendications 5 à 7, pour l'utilisation en thérapie.

10. Procédé de préparation d'un composé suivant la revendication 5 qui comprend
(a) la réaction d'un composé de structure (II) et un composé de structure (III):

40

45



(II)

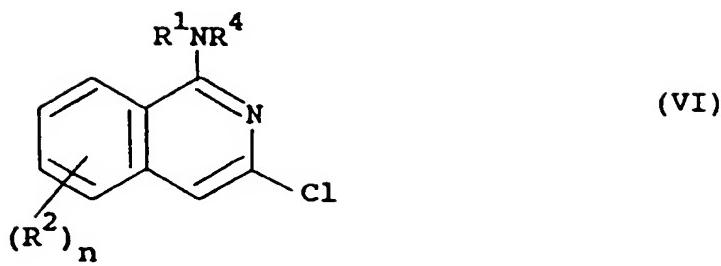
R¹R³NH (III)

50

dans lesquels R¹, R² et n sont tels que décrits pour la structure (IA), et X est un groupe déplaçable par une amine;

(b) pour les composés de structure (IA) dans lesquels une double liaison est présente, et dans lesquels R¹ est un groupe phényl(CH₂)_m éventuellement substitué et R³ est un atome d'hydrogène, la réaction d'un composé de structure (IV) avec un composé de structure (V):

(c) pour les composés de structure (IA) dans lesquels une double liaison est présente, la réduction d'un composé de structure (VI):



dans lequel R¹, R², et n sont tels que décrits pour la structure (IA); et R⁴ est un atome d'hydrogène ou un groupe azote protecteur;

et ensuite, si désiré,

- 15
- le déplacement de tout groupe protecteur;
 - la conversion d'un groupe R¹ en un autre groupe R¹;
 - la formation d'un sel acceptable du point de vue pharmaceutique.

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